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Effect of a single amino acid change in MHC class I molecules on the rate of progression to AIDS.

Gao X, Nelson GW, Karacki P, Martin MP, Phair J, Kaslow R, Goedert JJ, Buchbinder S, Hoots K, Vlahov D, O'Brien SJ, Carrington M.

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BACKGROUND: From studies of genetic polymorphisms and the rate of progression from human immunodeficiency virus type 1 (HIV-1) infection to the acquired immunodeficiency syndrome (AIDS), it appears that the strongest susceptibility is conferred by the major-histocompatibility-complex (MHC) class I type HLA-B*35,Cw*04 allele. However, cytotoxic T-lymphocyte responses have been observed against HIV-1 epitopes presented by HLA-B*3501, the most common HLA-B*35 subtype. We examined subtypes of HLA-B*35 in five cohorts and analyzed the relation of structural differences between HLA-B*35 subtypes to the risk of progression to AIDS. **METHODS:** Genotyping of HLA class I loci was performed for 850 patients who seroconverted and had known dates of HIV-1 infection. Survival analyses with respect to the rate of progression to AIDS were performed to identify the effects of closely related HLA-B*35 subtypes with different peptide-binding specificities. **RESULTS:** HLA-B*35 subtypes were divided into two groups according to peptide-binding specificity: the HLA-B*35-PY group, which consists primarily of HLA-B*3501 and binds epitopes with proline in position 2 and tyrosine in position 9; and the more broadly

reactive HLA-B*35-Px group, which also binds epitopes with proline in position 2 but can bind several different amino acids (not including tyrosine) in position 9. The influence of HLA-B*35 in accelerating progression to AIDS was completely attributable to HLA-B*35-Px alleles, some of which differ from HLA-B*35-PY alleles by only one amino acid residue.

CONCLUSIONS: This analysis shows that, in patients with HIV-1 infection, a single amino acid change in HLA molecules has a substantial effect on the rate of progression to AIDS. The different consequences of HLA-B*35-PY and HLA-B*35-Px in terms of disease progression highlight the importance of the epitope specificities of closely related class I molecules in the immune defense against HIV-1.

Publication Types:

- Multicenter Study

PMID: 11386265 [PubMed - indexed for MEDLINE]

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